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(54) Title: NOVEL HETEROCYCLIC COMPOUNDS			
(57) Abstract			
<p>The present invention relates to novel N-substituted azaheterocyclic compounds of general formula (I), wherein X, Y, Z, R¹, R² and m are as defined in the detailed part of the present description, or salts thereof, to methods for their preparation, to compositions containing them, and to their use for the clinical treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibers play a pathophysiological role by eliciting neurogenic pain or inflammation, as well as their use for treatment of indications caused by or related to the secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.</p>		<p style="text-align: right;">(I)</p>	

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NOVEL HETEROCYCLIC COMPOUNDS

FIELD OF INVENTION

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The present invention relates to novel N-substituted azaheterocyclic compounds in which a substituted alkyl chain forms part of the N-substituent or salts thereof, to methods for their preparation, to compositions containing them, to the use of the compounds for preparing compositions for the clinical treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role by eliciting neurogenic pain or inflammation, and to methods of treating said painful, hyperalgesic and/or inflammatory conditions. The invention also relates to the use of the present compounds for the treatment of insulin resistance in non-insulin-dependent diabetes mellitus (NIDDM) as well as ageing-associated obesity, the present compounds being known to interfere with neuropeptide containing C-fibres and hence to inhibit the secretion and circulation of insulin antagonising peptides like CGRP or amylin.

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BACKGROUND OF INVENTION

The nervous system exerts a profound effect on the inflammatory response. Antidromic stimulation of sensory nerves results in localised vasodilation and increased vascular permeability (Janecso et al. Br. J. Pharmacol. 1967, 31, 138-151), and a similar response is observed following injection of peptides known to be present in sensory nerves. From this and other data it is postulated that peptides released from sensory nerve endings mediate many inflammatory responses in tissues like skin, joint, urinary tract, eye, meninges, gastro-intestinal and respiratory tracts. Hence inhibition of sensory nerve peptide release and/or activity may be useful in treatment of for example arthritis, dermatitis, rhinitis, asthma, cystitis, gingivitis, thrombo-phlebitis, glaucoma, gastro-intestinal diseases or migraine.

Further, the potent effects of CGRP on skeletal muscle glycogen synthase activity and muscle glucose metabolism, together with the notion that this peptide is released from the neuromuscular junction by nerve excitation, suggest that CGRP may play a physiological role in skeletal muscle glucose metabolism by directing the phosphorylated glucose away from glycogen storage and into the glycolytic and oxidative pathways (Rossetti et al. Am. J.

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Physiol. 264, E1-E10, 1993). This peptide may represent an important physiological modulator of intracellular glucose trafficking in physiological conditions, such as exercise, and may also contribute to the decreased insulin action and skeletal muscle glycogen synthase in pathophysiological conditions like NIDDM or ageing-associated obesity (Melnyk
5 et al. Obesity Res. 3, 337-344, 1995) where circulating plasma levels of CGRP are markedly increased. Hence inhibition of release and/or activity of the neuropeptide CGRP may be useful in the treatment of insulin resistance related to type 2 diabetes or ageing.

In US Patent No. 4,383,999 and No. 4,514,414 and in EP 236342 as well as in EP 231996
10 some derivatives of N-(4,4-disubstituted-3-butenyl)azaheterocyclic carboxylic acids are claimed as inhibitors of GABA uptake. In EP 342635 and EP 374801, N-substituted azaheterocyclic carboxylic acids in which an oxime ether group and vinyl ether group forms part of the N-substituent respectively are claimed as inhibitors of GABA uptake. Further, in WO 9107389 and WO 9220658, N-substituted azacyclic carboxylic acids are claimed as
15 GABA uptake inhibitors. EP 221572 claims that 1-aryloxyalkylpyridine-3-carboxylic acids are inhibitors of GABA uptake.

EP 451772 and EP 406739 as well as Chem. Pharm. Bull. 42, 2285 (1994) discloses (dibenzo[a,d]cyclohepten-5-ylidene)piperidine derivatives and related compounds which
20 have antihistaminergic and antiallergic activity.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the general formulae I and Ia, wherein X, Y, Z,
25 R¹, R², R³ and m are as defined in the detailed part of the present description.

The present compounds are useful for the treatment, prevention, elimination, alleviation or amelioration of an indication related to all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role, e.g. neurogenic pain, neurogenic
30 inflammation, migraine, neuropathy, itching and rheumatoid arthritis, as well as indications caused by or related to the secretion and circulation of insulin antagonising peptides and other peptides derived from the sensory nervous system, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formulae or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

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In another aspect of the present invention there is provided a method of treating painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role, e.g. neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis, as well as a method of treating indications caused by or related to the
10 secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

The method of treatment may be described as the treatment, prevention, elimination, alleviation or amelioration of one of the above indications, which comprises the step of
15 administering to the said subject a neurologically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

A further aspect of the invention relates to the use of a compound of the present invention for the preparation of a pharmaceutical composition for the treatment of all painful, hyperalgesic
20 and/or inflammatory conditions in which C-fibres play a pathophysiological role, e.g. neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis, as well as for the treatment of indications caused by or related to the secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

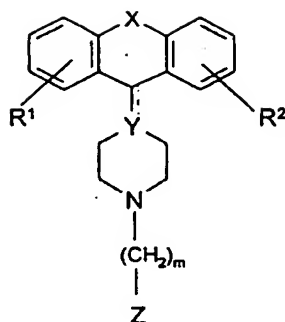
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Further objects will become apparent from the following description.

DETAILED DESCRIPTION OF THE INVENTION

30 Accordingly, the present invention relates to novel N-substituted azaheterocyclic compounds of the general formula I

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(I)

wherein R^1 and R^2 independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy;

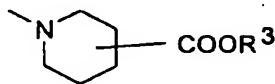
- 5 X is ortho-phenylene, -O-, -S-, $-C(R^6R^7)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10})CH_2-$, $-CH_2CH(R^{10})-$, $-(C=O)-$, $-N(R^9)-$ or $-(S=O)-$ wherein R^6 , R^7 , R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl, and wherein R^{10} is C_{1-6} -alkyl or phenyl;

- 10 Y is C or N;

___ is optionally a single bond or a double bond, and ___ is a single bond when Y is N;

m is 1, 2, 3, 4, 5 or 6; and

Z is $-COOR^3$ or



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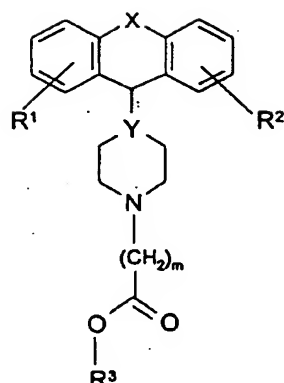
wherein R^3 is H or C_{1-6} -alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to the novel N-substituted azaheterocyclic compounds of

- 20 the general formula Ia

5



(Ia)

wherein R^1 and R^2 independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy;

- 5 X is ortho-phenylene, -O-, -S-, $-C(R^6R^7)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-$, $-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-$, $-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10})CH_2-$, $-CH_2CH(R^{10})-$, $-(C=O)-$, $-N(R^9)-$ or $-(S=O)-$ wherein R^6 , R^7 , R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl, and wherein R^{10} is C_{1-6} -alkyl or phenyl;

- 10 Y is C or N;

_____ is optionally a single bond or a double bond, and _____ is a single bond when Y is N;

m is 1, 2, 3, 4, 5 or 6; and

R^3 is H or C_{1-6} -alkyl;

or a pharmaceutically acceptable salt thereof.

15

Compounds of the general formulae wherein R^1 and R^2 are hydrogen; X is -O-, -S-, $-CH_2CH_2-$, $-CH=CH-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$; Y is C and _____ is a double bond; m is 1, 2, 3, 4, 5 or 6; Z is $-COOR^3$ and R^3 is H or C_{1-6} -alkyl are known from EP A 451772 and EP A 406739 as well as Chem. Pharm. Bull. 42, 2285 (1994) as compounds having

- 20 antihistaminergic and antiallergic activity.

The compounds according to the invention may exist as geometric and optical isomers and all isomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention. Isomers may be separated by means of standard
25 methods such as chromatographic techniques or fractional crystallisation of suitable salts.

Preferably, the compounds according to the invention exist as the individual geometric or optical isomers.

The compounds according to the invention may optionally exist as pharmaceutically acceptable acid addition salts, metal salts or, optionally alkylated, ammonium salts.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds according to the invention may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a lower alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free base forms.

In the above structural formulae and throughout the present specification, the following terms have the indicated meaning:

The term "C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms. Typical C₁₋₆-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, iso-hexyl, 4-methylpentyl, neopentyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like.

The term "C₁₋₆-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₆-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of
 5 linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

10

In a preferred embodiment of the invention R¹ and R² are selected from hydrogen, halogen, trifluoromethyl or C₁₋₆-alkyl. Preferably R¹ and R² are hydrogen.

In another preferred embodiment of the invention Y is N.

15

In another preferred embodiment of the invention Y is C and ____ is a double bond.

In another preferred embodiment of the invention X is selected from -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-. Preferably X is -CH₂CH₂-.

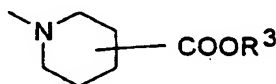
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In another preferred embodiment of the invention X is -S-CH₂- or -CH₂-S-.

In another preferred embodiment of the invention m is 1, 2, 3 or 4.

25 In another preferred embodiment of the invention Z is -COOR³.

In another preferred embodiment of the invention Z is



30

In yet another preferred embodiment of the invention R³ is H.

Preferred compounds of the present invention include:

2-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)acetic acid,

3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)propionic acid,

5

4-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)butyric acid,

5-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)pentanoic acid,

10 or a pharmaceutically acceptable salt thereof.

Other preferred compounds of the present invention include:

15 1-(3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidiny)-1-propyl)-3-piperidinecarboxylic acid,

(R)-1-(2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)piperidin-1-yl)ethyl)-3-piperidinecarboxylic acid,

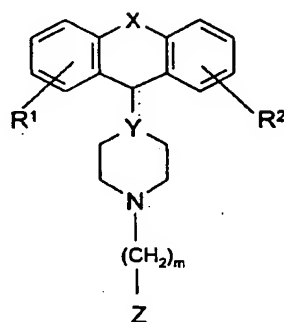
20 or a pharmaceutically acceptable salt thereof.

It has been demonstrated that the compounds according to the invention inhibit neurogenic inflammation which involves the release of neuropeptides from peripheral and central endings of sensory C-fibres. Experimentally this can be demonstrated in animal models of
25 histamine induced paw oedema Amann et al. (Europ. J. Pharmacol. 279, 227-231, 1995) in which the compounds according to the invention exhibit a potent inhibitory effect. The compounds according to the invention may be used to treat all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role by eliciting neurogenic pain or inflammation, i.e.:

30 Acutely painful conditions exemplified by migraine, postoperative pain, burns, bruises, post-herpetic pain (Zoster) and pain as it is generally associated with acute inflammation; chronic, painful and/or inflammatory conditions exemplified by various types of neuropathy (diabetic, post-traumatic, toxic), neuralgia, rheumatoid arthritis, spondylitis, gout, inflammatory bowel disease, prostatitis, cancer pain, chronic headache, coughing, asthma, itching, chronic

pancreatitis, inflammatory skin disease including psoriasis and autoimmune dermatoses, osteoporotic pain.

Also included within the present invention are the use of the compounds of the general formula I



(I)

wherein R¹ and R² are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

Y is C and ... is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl,

or a pharmaceutically acceptable salt thereof, for the preparation of pharmaceutical

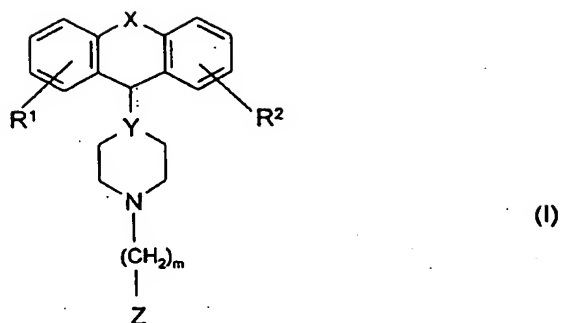
compositions for the treatment of neurogenic inflammation, painful and/or inflammatory conditions e.g. neuropathy and rheumatoid arthritis.

Further, it has been demonstrated that the compounds according to the invention improves the glucose tolerance in diabetic ob/ob mice and that this may result from the reduced release of CGRP from peripheral nervous endings. Hence the compounds according to the invention may be used in the treatment of NIDDM as well as ageing-associated obesity. Experimentally this has been demonstrated by the subcutaneous administration of glucose into ob/ob mice with or without previous oral treatment with a compound according to the invention.

25

Also included within the present invention are the use of the compounds of the general formula I

10



wherein R^1 and R^2 are hydrogen;

X is $-O-$, $-S-$, $-CH_2CH_2-$, $-CH=CH-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$;

5 Y is C and --- is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is $-COOR^3$ and R^3 is H or C_{1-6} -alkyl,

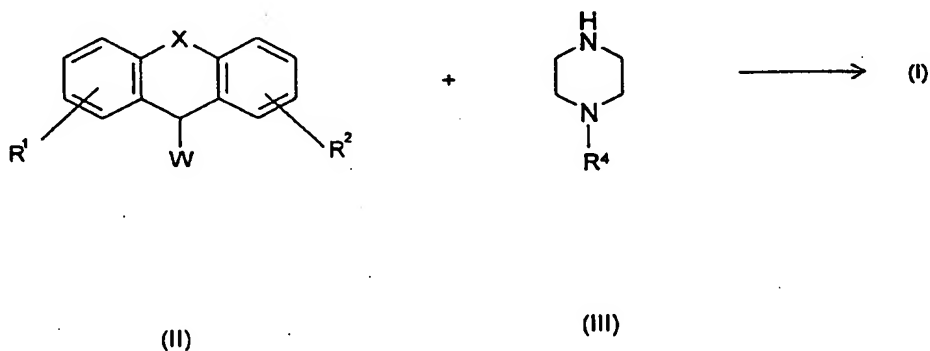
or a pharmaceutically acceptable salt thereof, for the preparation of pharmaceutical

compositions for reducing blood glucose. Hence these compounds may be used in the

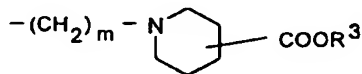
10 treatment non-insulin-dependent diabetes mellitus (NIDDM), as well as in the treatment of insulin resistance in NIDDM.

The compounds of the general formula I, wherein Y is N , may be prepared by the following

15 methods:



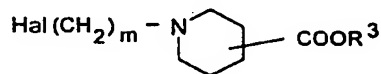
A compound of formula II wherein R^1 , R^2 and X are as defined above and W is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate may be reacted with a piperazine of formula III wherein R^4 is hydrogen, a suitable N-protecting group, $-(CH_2)_m-CO_2R^3$ or



5 wherein R^3 is as defined above. Introduction and removal of such groups is described in "Protective Groups in Organic Chemistry" J.F.W. McOrnie ed. (New York, 1973).

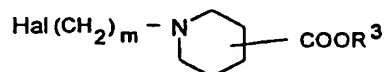
This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, dioxane, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a base e.g. sodium hydride or potassium carbonate and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h.

When R^4 in formula III is hydrogen, a second N-alkylation with a compound $Hal(CH_2)_m-CO_2R^3$ or



follows, where Hal means a halogen and R^3 and m are as defined above.

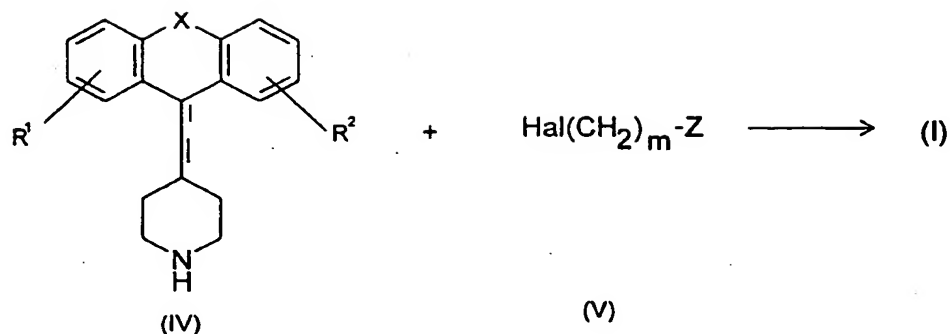
When R^4 in formula III is a protecting group then, after deprotection, a second N-alkylation with a compound $Hal(CH_2)_m-CO_2R^3$ or



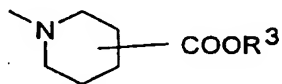
follows. When R^3 is an C_{1-6} -alkyl group, a final deprotection step may be performed.

The compounds of the general formula I, wherein Y is C, may be prepared by the following methods:

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A compound of formula IV wherein R^1 , R^2 and X are as defined may be reacted with a compound of formula V, where Hal means a halogen, Z means $-\text{COOR}^3$ or



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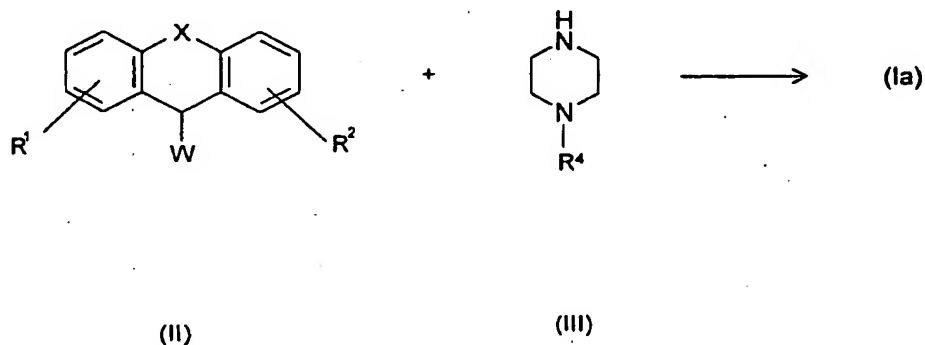
and R^3 and m are as defined above. This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, dioxane, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a base e.g. sodium hydride or potassium carbonate and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h.

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When R^3 is an C_{1-6} -alkyl group, a final deprotection step may be performed.

15

The compounds of formula Ia, wherein Y is N, may be prepared by the following methods:



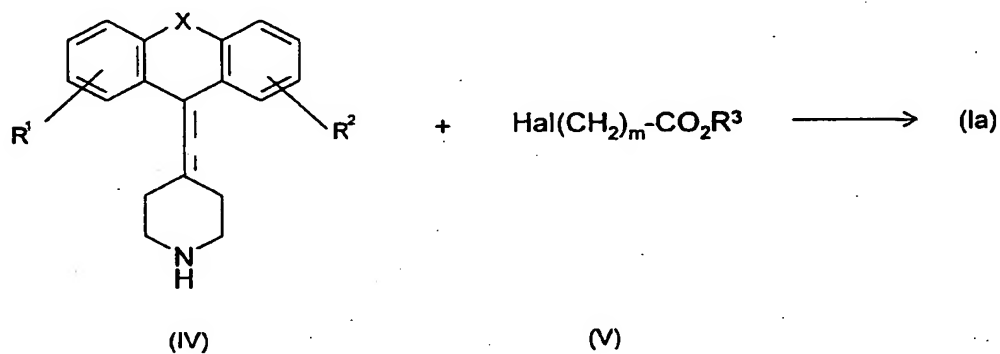
A compound of formula II wherein R^1 , R^2 and X are as defined above and W is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate may be reacted with a piperazine of formula III wherein R^4 is hydrogen, a suitable N-protecting group or $-(CH_2)_m-$
 5 CO_2R^3 wherein R^3 is as defined above. Introduction and removal of such groups is described in "Protective Groups in Organic Chemistry" J.F.W. McOrnie ed. (New York, 1973).

This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, dioxane, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a
 10 base e.g. sodium hydride or potassium carbonate and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h.

When R^4 in formula III is hydrogen, a second N-alkylation with a compound $Hal(CH_2)_m-CO_2R^3$ follows, where Hal means a halogen and R^3 and m are as defined above.

15 When R^4 in formula III is a protecting group then, after deprotection, a second N-alkylation with a compound $Hal(CH_2)_m-CO_2R^3$ follows. When R^3 is an C_{1-6} -alkyl group, a final deprotection step may be performed.

20 Compounds of formula Ia, wherein Y is C, may be prepared by the following methods:



A compound of formula IV wherein R^1 , R^2 and X are as defined may be reacted with a
 25 compound of formula V, where Hal means a halogen and R^3 and m are as defined above. This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, dioxane, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a

base e.g. sodium hydride or potassium carbonate and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h.

When R³ is an C₁₋₆-alkyl group, a final deprotection step may be performed.

5

Compounds of formula IV and V may readily be prepared by methods familiar to those skilled in the art.

PHARMACOLOGICAL METHODS

10

I. Histamine induced paw oedema

The rat histamine paw oedema test was performed essentially as described by Amann et al. (Europ. J. Pharmacol. 279, 227-231, 1995). In brief 250-300 g male Sprague-Dawley rats were anaesthetized with pentobarbital sodium, and placed on a 32 degree heated table. Ten minutes later histamine (50 micoliter, 3 mg/ml) was injected in the right hind paw and 20 minutes hereafter the paw swelling was determined by water plethysmography (Ugo Basile). Test compounds were administered intraperitoneally at 15 minutes before the anaesthetics.

20

II. Histamine induced hyperglycemia in mice

Conscious unfasted 25 g male NMRI mice are administered histamine chloride (90 nmol) icv according to the method of Nishibori et al. (J. Pharmacol. Exp. Therap. 241, 582-286, 1987). Blood glucose is determined at time 0 and 40 min after the histamine injection. Test compounds are administered at 1.0 mg/kg ip 30 min before the histamine injection, and % inhibition refers to the capacity of the compounds to inhibit the histamine induced blood glucose rise.

30

III. Reduced release of CGRP

ob/ob female mice, 16 weeks of age, where injected glucose (2g/kg) subcutaneously. At times hereafter blood glucose was determined in tail venous blood by the glucose oxidase method. At the end of the study the animals were decapitated and trunk blood collected.

Immunoreactive CGRP was determined in plasma by radio-immuno-assay. Two groups of animals were used. The one group was vehicle treated, whereas the other group received a compound of formula I via drinking water (100 mg/l) for five days before the test.

5

Values for inhibition of histamine induced oedema response for a representative compound is listed in table I.

TABLE I

10

Inhibition of histamine induced paw oedema at 1.0 mg/kg

Example no.	% inhibition
2	44
10	33

15

Values for inhibition of histamine induced hyperglycemia for a representative compound is listed in table II.

TABLE II

20

Inhibition of histamine induced hyperglycemia at 1.0 mg/kg

Example no.	% inhibition
10	69

PHARMACEUTICAL COMPOSITIONS

25

The present invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the invention or a pharmaceutically acceptable

salt thereof and, usually, such compositions also contain a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions comprising a compound of the present invention may be
5 prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention or a pharmaceutically acceptable
10 acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier,
15 or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols,
20 polyhydroxyethoxylated castor oil, syrup, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include
25 any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by
30 employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, topical, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	

Coating:

HPMC approx.

9 mg

*Mywacett 9-40 T approx.

0.9 mg

5

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of an indication related to all painful, hyperalgesic and/or inflammatory conditions in which C-fibres play a pathophysiological role such as e.g. neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis, as well as indications caused by or related to the secretion and circulation of insulin antagonising peptides, such as non-insulin-dependent diabetes mellitus (NIDDM) or ageing-associated obesity. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, in an effective amount.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of humans, dosages from about 0.5 to about 1000 mg, preferably from about 1 to about 500 mg of compounds of the present invention, conveniently given from 1 to 5 times daily. A most preferable dosage is from about 50 to about 200 mg per dose when administered to e.g. a human. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 50 to about 200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

5

The method of treating may be described as the treatment of an indication caused by or related to the secretion and circulation of insulin antagonising peptides like CGRP or amylin in a subject in need thereof, which comprises the step of administering to the said subject a neurologically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

10

Any novel feature or combination of features described herein is considered essential to this invention.

15

EXAMPLES

The process for preparing compounds of the present invention and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

20

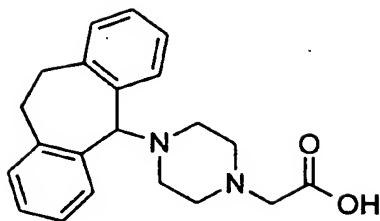
Hereinafter, TLC is thin layer chromatography, CDCl_3 is deuterio chloroform and $\text{DMSO}-d_6$ is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^1H NMR shifts (δ_{H}) are given in parts per million (ppm). M.p. is melting point and is given in $^{\circ}\text{C}$ and is not corrected. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. (1978), 43, 2923-2925 on Merck silica gel 60 (Art. 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

25

30

EXAMPLE 1

2-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)acetic acid



5-Chlorodibenzosuberane (10.0 g, 43 mmol) and piperazine (18.0 g, 218 mmol) was suspended in 1,4-dioxane (300 ml) and heated at reflux temperature for 6 h. The reaction mixture was cooled to room temperature and filtered. To the filtrate water (300 ml) was added, pH was adjusted to 10 with saturated sodium hydrogen carbonate and the mixture was extracted with dichloromethane (3 x 75 ml). The combined organic extracts were washed with water (150 ml), dried (MgSO₄) and concentrated *in vacuo*. Dichloromethane (50 ml) was added, and the solution was filtered. The filtrate was subjected to column chromatography on silica gel (130 g) by first eluting with dichloromethane (150 ml) and then dichloromethane/methanol = 9:1 (250 ml). This furnished 4.5 g of crude product which was recrystallised from heptane affording 4.2 g (33 %) of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine.

¹H-NMR (300 MHz, CDCl₃) δ 7.10 (m, 8H), 4.00 (m, 2H), 3.95 (s, 1H), 2.75 (m, 6H), 2.25 (s, 4H).

The piperazine from the step above (1.0 g, 3.6 mmol), ethyl 2-chloroacetate (0.5 g, 4.0 mmol), and potassium carbonate (0.5 g, 4 mmol) were suspended in acetonitrile (50 ml) and allowed to react at 50 °C for 4 h. The crude reaction mixture was subjected to column chromatography on silica gel (30 g) by first eluting with dichloromethane (50 ml) and then dichloromethane/methanol = 9:1 (250 ml). This furnished 1.05 g (73 %) of 2-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)acetic acid ethyl ester.

¹H-NMR (300 MHz, CDCl₃) δ 7.0 (m, 8H), 4.13 (q, 2H), 2.95 (m, 3H), 3.10 (s, 2H), 2.74 (m, 2H), 2.40 (d, 8H), 1.20 (t, 3H).

The ester from the above step (1.05 g, 2.9 mmol), sodium hydroxide (0.8 g, 20 mmol) and water (2 ml) was dissolved in ethanol (50 ml) and allowed to react at 50 °C for 2 h. After

cooling to room temperature, water (150 ml) was added and the reaction mixture was adjusted to pH 2 with 1 N hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The resulting oil was stripped with acetone (2 x 20 ml), dissolved in dichloromethane (20 ml) and precipitated with petroleum ether. The resulting solid was dried under vacuum for 24 h leaving the title compound (0.56 g, 57 %).

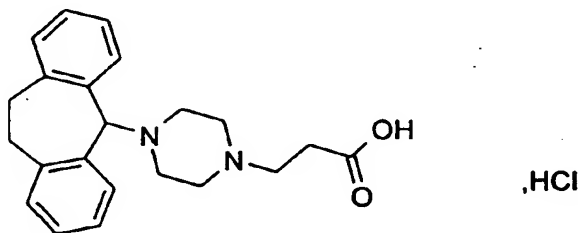
HPLC retention time = 17.55 minutes (5µm C18 4 x 250 mm column, eluting with a 20-80 % gradient of 0.1 % trifluoroacetic acid/acetonitrile and 0.1 % trifluoroacetic acid/water over 30 minutes at room temperature).

¹H-NMR (300 MHz, CDCl₃) δ 7.10 (m, 8H), 4.12 (s, 1H), 3.87 (m, 2H), 3.63 (s, 2H), 3.22 (bs, 4H), 2.80 (m, 2H), 2.65 (s, 4H).

15

EXAMPLE 2

3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)propionic acid hydrochloride



20

1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine (prepared as described in Example 1, 1.0 g, 3.6 mmol), ethyl 3-bromopropionate (0.71 g, 3.9 mmol), and potassium carbonate (0.5 g, 4 mmol) were suspended in acetonitrile (50 ml) and allowed to react at 50 °C for 4 h. The crude reaction mixture was subjected to column chromatography on silica gel (30 g) by first eluting with dichloromethane (50 ml) and then dichloromethane/methanol = 9:1 (250 ml). This furnished 1.15 g (84 %) of 3-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)propionic acid ethyl ester.

¹H-NMR (300 MHz, CDCl₃) δ 7.10 (m, 8H), 4.13 (q, 2H), 2.95 (m, 3H), 2.77 (m, 2H), 2.62 (t, 2H), 2.41 (t, 2H), 2.30 (bd, 8H) 1.20 (t, 3H).

The ester from the above step (1.15 g, 3.0 mmol), sodium hydroxide (0.8 g, 20 mmol) and water (2 ml) were dissolved in ethanol (50 ml) and allowed to react at 50 °C for 2 h. After cooling to room temperature, water (150 ml) was added, and the reaction mixture was adjusted to pH 2 with 1 N hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The resulting oil was stripped with acetone (2 x 20 ml), reprecipitated from acetone and dried under vacuum for 24 h leaving the title compound (0.80 g, 69 %) as an amorphous solid.

Calculated for C₂₂H₂₆N₂O₂·HCl:

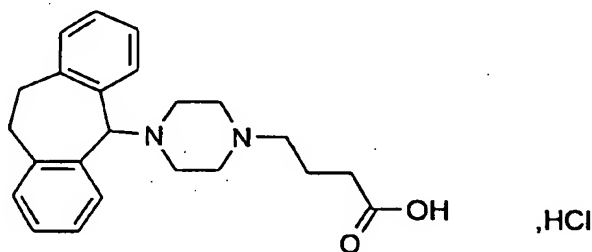
C, 68.55 %; H, 7.05 %; N, 7.27 %; Found:

C, 68.29 %; H, 7.03 %; N, 7.24 %.

¹H-NMR (300 MHz, CDCl₃) δ 7.10 (m, 8H), 4.17 (s, 1H), 3.88 (m, 2H), 3.50 - 3.10 (bs, 2H), 3.29 (t, 2H), 2.93 (t, 2H), 2.80 (m, 2H), 2.72 (s, 6H).

EXAMPLE 3

4-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)butyric acid hydrochloride



1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine (prepared as described in Example 1, 1.0 g, 3.6 mmol), ethyl 4-bromobutyrate (0.76 g, 3.9 mmol), and potassium carbonate (0.5 g, 4 mmol) were suspended in acetonitrile (50 ml) and allowed to react at 50 °C for 3 h. The crude reaction mixture was subjected to column chromatography on silica gel

(30 g) by first eluting with dichloromethane (50 ml) and then dichloromethane/methanol = 9:1 (250 ml). This furnished 1.2 g (85 %) of 4-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-yl)piperazin-1-yl)butyric acid ethyl ester.

- 5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.10 (m, 8H), 4.09 (q, 2H), 2.95 (m, 3H), 2.78 (m, 2H), 2.30 (m, 12H), 1.76 (m, 2H), 1.20 (t, 3H).

- The ester from the above step (1.2 g, 3.0 mmol), sodium hydroxide (0.8 g, 20 mmol) and water (2 ml) were dissolved in ethanol (50 ml) and allowed to react at 50 $^\circ\text{C}$ for 3 h. After
10 cooling to room temperature, water (150 ml) was added and the reaction mixture was adjusted to pH 2 with 1 N hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo. The resulting oil was stripped with acetone (2 x 20 ml), washed with acetone (20 ml) and dried under vacuum for 24 h leaving the title compound (0.93 g, 77%) as an amorphous solid.

15

Calculated for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2$, HCl:

C, 68.80 %; H, 7.33 %; N, 6.89 %; Found:

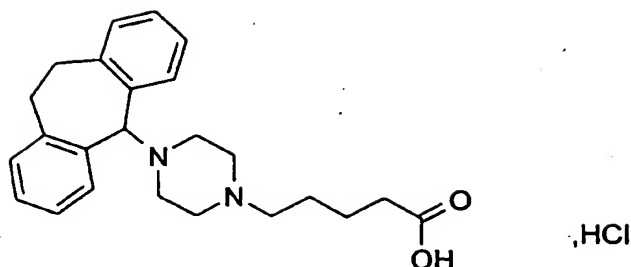
C, 68.90 %; H, 7.29 %; N, 6.99 %.

- 20 $^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 12.3 (s, 1H), 11.0 (s, 1H), 7.15 (m, 8H), 4.17 (s, 1H), 3.89 (m, 2H), 3.36 (d, 3H (+ H_2O)), 2.9 (m, 4H), 2.74 (q, 2H), 2.50 (m, 5H (+DMSO)), 2.30 (t, 2H), 1.87 (m, 2H).

EXAMPLE 4

25

5-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)pentanoic acid hydrochloride



1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine (1.0 g, 3.6 mmol), methyl 5-bromovalerate (0.80 g, 4.0 mmol), and potassium carbonate (0.5 g, 4 mmol) were suspended in acetonitrile (50 ml) and allowed to react at 50 °C for 4 h. The crude reaction mixture was subjected to column chromatography on silica gel (30 g) by first eluting with dichloromethane (50 ml) and then dichloromethane/methanol = 9:1 (250 ml). This furnished 1.2 g (77 %) of 5-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl)-pentanoic acid methyl ester.

¹H-NMR (300 MHz, CDCl₃) δ 7.10 (m, 8H), 4.0 (m, 2H), 2.94 (s, 1H), 3.63 (s, 3H), 2.75 (m, 2H), 2.30 (m, 12H), 1.60 (m, 2H), 1.46 (m, 2H).

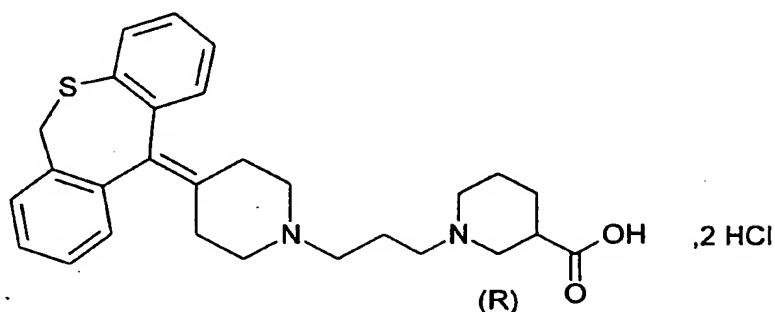
The ester from the above step (1.2 g, 3.0 mmol), sodium hydroxide (0.8 g, 20 mmol) and water (2 ml) was dissolved in ethanol (50 ml) and allowed to react at 50 °C for 3 h. After cooling to room temperature, water (150 ml) was added and the reaction mixture was adjusted to pH 2 with 1 N hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The resulting oil was stripped with acetone (2 x 20 ml), washed with acetone (20 ml) and dried under vacuum for 24 h leaving the title compound (1.02 g, 80 %) as an amorphous solid.

HPLC retention time = 17.55 minutes (5 µm C18 4 x 250 mm column, eluting with a 20-80 % gradient of 0.1 % trifluoroacetic acid/acetonitrile and 0.1 % trifluoroacetic acid/water over 30 minutes at room temperature)

¹H-NMR (300 MHz, DMSO-*d*₆) δ 12.1 (s, 1H), 10.8 (s, 1H), 7.10 (m, 8H), 4.16 (s, 1H), 3.87 (m, 2H), 3.32 (d, 3H), 2.95 (m, 4H), 2.73 (m, 2H), 2.59 (d, 2H), 2.40 (m, 3H), 2.24 (t, 2H), 1.75 (m, 2H), 1.46 (t, 2H).

EXAMPLE 5

1-(3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidinyl)-1-propyl)-3-piperidinecarboxylic acid dihydrochloride



To a solution of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine (5.86 g, 20 mmol, prepared similarly as described in Ger. Offen 2 423 721) in 2-butanone (60 ml), potassium carbonate (4.2 g, 30 mmol) and 3-bromo-1-propyl tetrahydro-2-pyranyl ether (5.75 g, 25.8 mmol) were added and the reaction mixture was heated at reflux temperature for 20 h. After cooling to room temperature the mixture was filtered and the filtrate was evaporated. The residue was dissolved in a mixture of methanol (60 ml) and 5 N hydrochloric acid (20 ml). The solution was heated at reflux temperature for 15 minutes, methanol was distilled off and water (100 ml) followed by 5 N sodium hydroxide (40 ml) were added. The mixture was extracted with benzene, the organic extract was dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (50 g) using ethyl acetate as eluent. This afforded 6.3 g (90 %) of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidinepropanol as an oil.

TLC: R_f = 0.35 (SiO_2 : chloroform/ethanol/ammonium hydroxide = 20:1:0.1)

The above alcohol (5.8 g, 16.5 mmol) was dissolved in benzene (60 ml), triethylamine (5 ml) and methanesulfonyl chloride (2.25 g, 19.6 mmol) were added and the reaction mixture was stirred for 5 h. After standing for 8 days, water (100 ml) was added and the phases were separated. The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue (2.25 g) was dissolved in 2-butanone (50 ml), and (R)-3-piperidinecarboxylic

acid ethyl ester tartrate (1.6 g, 5.3 mmol) and potassium carbonate (3.0 g, 21.7 mmol) were added and the mixture was heated at reflux temperature for 20 h. After filtration the solvent was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (40 g) using ethanol as eluent. This afforded 1.7 g (22 %) of 1-(3-(4-(6,11-dihydrodibenzo[b,e]-thiepin-11-ylidene)-1-piperidinyl)-1-propyl)-3-piperidinecarboxylic acid ethyl ester as an oil.

TLC: R_f = 0.22 (SiO₂: chloroform/ethanol/ammonium hydroxide = 20:3:0.1)

The above ester (0.86 g, 1.8 mmol) was dissolved in ethanol (30 ml) and 5 N sodium hydroxide (2 ml) was added. The mixture was stirred at 40 °C for 24 h, ethanol was evaporated in vacuo and the residue was dissolved in water. Acetic acid (2 ml) was added and the mixture was extracted with dichloromethane (50 ml). After drying (MgSO₄), the solvent was evaporated in vacuo. The residue was triturated with diethyl ether affording 0.42 g (52 %) of the title compound as an amorphous solid. The corresponding dihydrochloride was prepared by dissolving the base in acetone (5 ml) and treating the mixture with hydrogen chloride in diethyl ether. After dilution with ether (20 ml), filtration and drying, the dihydrochloride was obtained.

M.p. 245 -255 °C (decomp.)

Calculated for C₂₈H₃₄N₂O₂S, 2 HCl, 0.25 H₂O:

C, 62.79 %; H, 6.78 %; Cl, 13.24 %; N, 5.23 %; S, 5.99 %; Found:

C, 62.33 %; H, 6.84 %; Cl, 11.99 %; N, 4.96 %; S, 6.38 %.

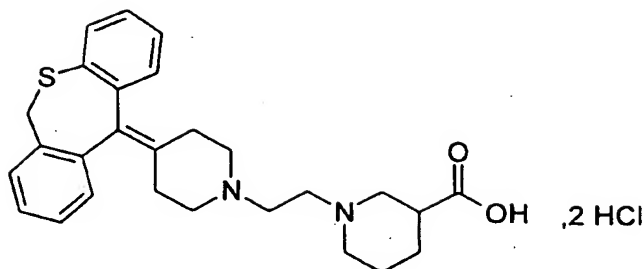
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EXAMPLE 6

(R)-1-(2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)piperidin-1-yl)ethyl)-3-piperidinecarboxylic acid dihydrochloride

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A mixture of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine hydrochloride (5.98 g, 18.1 mmol), 2-bromethanol (2.75 g, 22 mmol), potassium carbonate (6.0 g, 43.5 mmol) and acetone (100 ml) was stirred and heated at reflux temperature for 8 h. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (40 g) using a mixture of chloroform and ethanol (10:1) as eluent. This afforded 1.6 g (34 %) of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidineethanol as an oil.

TLC: R_f = 0.31 (SiO_2 ; chloroform/ethanol/ammonia = 20:1 :0.05).

The above alcohol (1.6 g, 4.74 mmol) was dissolved in benzene (30 ml) and triethylamine (3 ml) was added. Methanesulfonyl chloride (0.8 g, 7 mmol) was added and the reaction mixture was stirred for 2 h. Water (50 ml) was added and the phases were separated. The organic phase was dried (MgSO_4) and the solvent evaporated *in vacuo*, affording a residue which was dissolved in N,N-dimethylformamide (10 ml). (R)-3-Piperidinecarboxylic acid ethyl ester tartrate (1.6 g, 5.2 mmol) and potassium carbonate (1.5 g, 10.8 mmol) were added and the mixture was heated at 100 °C for 11 h. Benzene (100 ml) and water (100 ml) were added and the phases were separated. The organic phase was dried (K_2CO_3) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20 g) using first ethyl acetate and then ethanol as eluents. This afforded 1.3 g (58 %) of (R)-1-(2-(4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidin-1-yl)ethyl)-3-piperidinecarboxylic acid ethyl ester as an oil.

TLC: R_f = 0.20 (SiO_2 ; chloroform/ethanol/ammonia = 20:3:0.05).

The above ester (1.3 g, 2.7 mmol) was dissolved in ethanol (20 ml) and 5 N sodium hydroxide (2 ml) was added. The mixture was stirred at room temperature for 72 h, ethanol was

evaporated in vacuo and water (40 ml) was added. The mixture was extracted with diethyl ether (40 ml) and the phases were separated. Acetic acid (2 ml) was added to the water phase and the mixture was extracted with dichloromethane (50 ml). The organic phase was dried (MgSO_4) and the solvent was evaporated in vacuo. The residue was dissolved in acetone and neutralised with hydrogen chloride in diethyl ether. The precipitate was filtered off and crystallised from a mixture of ethanol, acetone and diethyl ether to give 0.47 g (30 %) of the title compound as a solid.

M.p. 127 - 130 °C.

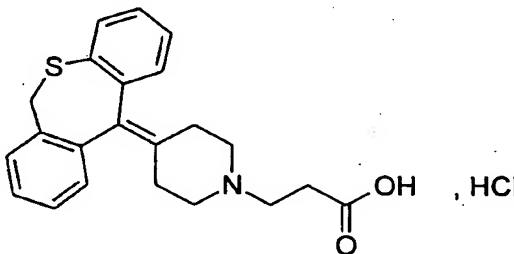
Calculated for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$, 2 HCl, H_2O , 0.5 CH_3COCH_3 :

C, 60.20 %; H, 6.91 %; N, 4.93 %; S, 5.64 %; Found:

C, 60.11 %; H, 6.78 %; N, 4.91 %; S, 5.55%.

EXAMPLE 7

3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidine)propionic acid hydrochloride:



20

A mixture of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine (4.0 g, 0.0136 mol, prepared similarly as described in Ger. Offen 2 423 721) and ethyl acrylate (2.45 g, 0.0245 mol) in ethanol (50 ml) was heated at 70 °C for 2 h. The volatile materials were evaporated in vacuo and the residue (5.0 g) was dissolved in ethanol (25 ml) and neutralised with solution of oxalic acid in ethanol. Diethyl ether (30 ml) was added and the precipitated hydrogen oxalate was filtered off, washed with diethyl ether and crystallised from a mixture of ethanol and ether. After filtration and drying, this afforded 5.6 g (91 %) of 3-(4-(6,11-

dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidine)propionic acid ethyl ester hydrogen oxalate.

A mixture of 3-(4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidine)propionic acid ethyl ester (liberated from the above hydrogen oxalate, 3.0 g, 0.0076 mol) was dissolved in ethanol (40 ml) and 4 N sodium hydroxide (10 ml) was added. The reaction mixture was stirred at room temperature for 10 h; then poured into dichloromethane (300 ml) and acidified with concentrated hydrochloric acid. The dichloromethane layer was separated, dried (MgSO₄) and evaporated in vacuo. The oily residue was re-evaporated twice with acetone and triturated with hot acetone to give 2.3 g (75 %) of the title compound as an amorphous solid.

M.p. 176 - 186 °C (decomp.)

15 Calculated for C₂₂H₂₃NO₂S, HCl, 0.25 H₂O:

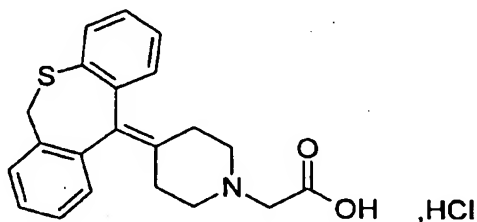
C, 65.01 %; H, 6.08 %; Cl, 8.72 %; N, 3.45 %; S, 7.89 %; Found:

C, 65.13 %; H, 6.13 %; Cl, 8.62 %; N, 3.46 %; S, 7.92 %.

EXAMPLE 8

20

2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidinyl)acetic acid hydrochloride



25 To a solution of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine (8.66 g, 0.0295 mol) in N,N-dimethylformamide (36 ml), ethyl bromoacetate (4.93 g, 0.0295 mol) and potassium carbonate (9.75 g, 0.0885 mol) were added and the reaction mixture was heated at 63 - 66 °C for 4.5 h. Water (250 ml) was added followed by benzene (150 ml). The phases were separated and the organic phase was washed with water (3 x 50 ml) and dried (MgSO₄).

30 After evaporation in vacuo the residue was purified by column chromatography on silica gel

(140 g) using benzene and a mixture of benzene and chloroform (1:1) as eluents. This afforded 3.26 g (29 %) 2-(4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-piperidin-1-yl)acetic acid ethyl ester as an oil.

5 TLC: R_f = 0.48 (SiO₂: chloroform saturated with ammonia/ethanol = 20:1)

To a solution of the above ester (3.26 g, 0.00859 mol) in ethanol (70 ml), 4 N sodium hydroxide (10 ml) was added and the reaction mixture was stirred at room temperature overnight. Concentrated hydrochloric acid (4.8 ml) and dichloromethane (480 ml) were added
10 and the reaction mixture was shaken well. The phases were separated and the organic layer was dried (MgSO₄) and evaporated *in vacuo*. This was followed by re-dissolution and evaporation from acetone (2 x 100 ml). The residue was stirred with boiling acetone (300 ml), cooled and the precipitate was filtered to give 2.44 g (71.5 %) of the title compound as a solid.

15

M.p. 170-175 °C.

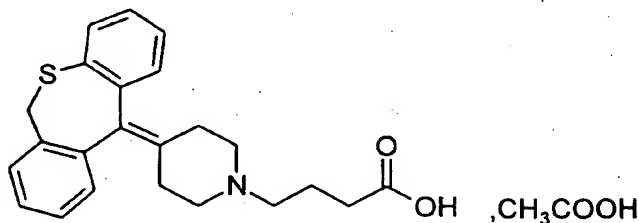
Calculated for C₂₁H₂₁NO₂S, HCl, 0.5 H₂O:

C, 63.54 %; H, 5.84 %; N, 3.53 %; Cl, 8.93 %; S, 8.08 %; Found:

20 C, 63.25 %; H, 5.67 %; N, 3.62 %; Cl, 9.14 %; S, 8.04 %.

EXAMPLE 9

4-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidinyl)butyric acid acetate



A mixture of 4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine hydrochloride (4.35 g, 13.2 mmol), 4-chlorobutyric acid ethyl ester (3.4 g, 24.2 mmol), potassium carbonate (4.0 g, 29 mmol), sodium iodide (1 g) and acetone (100 ml) was stirred and heated at reflux temperature for 14 h. The mixture was filtered and the filtrate evaporated *in vacuo* to give a resi-
30

due which was purified by chromatography on silica gel (50 g) using chloroform as eluent. This afforded 2.85 g of 4-(4-(6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)piperidine)-butyric acid ethyl ester as an oil.

5 TLC: $R_f = 0.55$ (SiO_2 : benzene/diethyl ether/ethanol = 10:10:2)

The above ester (2.85 g, 7 mmol) was dissolved in ethanol (50 ml) and 5 N sodium hydroxide (3 ml) was added. The mixture was stirred at room temperature for 20 h, ethanol was evaporated in vacuo and water (40 ml) was added. The mixture was extracted with diethyl
10 ether (40 ml) and the phases were separated. Acetic acid (3 ml) was added to the aqueous phase and the mixture was extracted with dichloromethane (50 ml). The organic phase was dried (MgSO_4) and the solvent was evaporated in vacuo. The residue was triturated with diethyl ether and the precipitate was filtered off and dried to give 2.0 g (62 %) of the title compound as an amorphous solid.

15

Calculated for $\text{C}_{23}\text{H}_{25}\text{NO}_2\text{S}$, CH_3COOH :

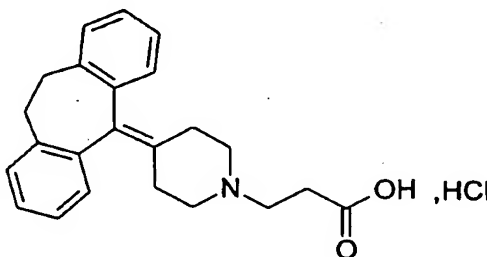
C, 68.31 %; H, 6.65 %; N, 3.19 %; S, 7.29 %; Found:

C, 68.36 %; H, 6.77 %; N, 3.12 %; S, 7.39 %.

20

EXAMPLE 10

3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine)propionic acid hydrochloride



25

A mixture of 4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (2.75 g, 0.01 mol) and ethyl acrylate (2.0 g, 0.02 mol) in ethanol (50 ml) was heated at 70 °C for 2 h. Volatile components were evaporated in vacuo, the residue (4.4 g) was dissolved in diethyl ether

(50 ml) and the mixture was neutralised with a solution of oxalic acid (1.26 g) in ethanol (8 ml). The precipitated hydrogen oxalate was filtered off, washed with diethyl ether and crystallised from a mixture of ethanol and ether. After filtration and drying, this afforded 3.9 g (89 %) of 3-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine)propionic acid ethyl ester hydrogen oxalate.

3-(4-(10,11 -Dihydro-5H-dibenzo[a,d]cyclohept-5-ylidene)-1-piperidine)propionic acid ethyl ester (liberated from the above hydrogen oxalate, 3.1 g, 0.00826 mol) was dissolved in ethanol (20 ml) and 4 N sodium hydroxide (6 ml) was added. The reaction mixture was stirred at room temperature for 10 h, then poured into dichloromethane (300 ml) and acidified with concentrated hydrochloric acid to pH = 1. The dichloromethane layer was separated, dried (MgSO₄) and evaporated in vacuo. The oily residue was re-evaporated twice with acetone and then triturated with hot acetone. This afforded 2.55 g (80 %) of the title compound as a solid.

15

M.p. 203 - 205 °C.

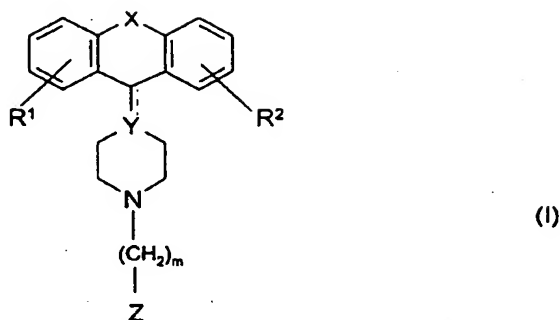
Calculated for C₂₃H₂₅NO₂, HCl:

C, 71.96 %; H, 6.83 %; Cl, 9.23 %; N, 3.65 %; Found:

20 C, 71.57 %; H, 7.00 %; Cl, 9.01 %; N, 3.73 %.

CLAIMS

1. A compound of formula I



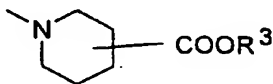
5

wherein R^1 and R^2 independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy;

- X is ortho-phenylene, -O-, -S-, $-C(R^6R^7)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-$, $(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-$, $-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10})CH_2-$, $-CH_2CH(R^{10})-$, $-(C=O)-$, $-N(R^8)-$ or $-(S=O)-$ wherein R^6 , R^7 , R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl, and wherein R^{10} is C_{1-6} -alkyl or phenyl;

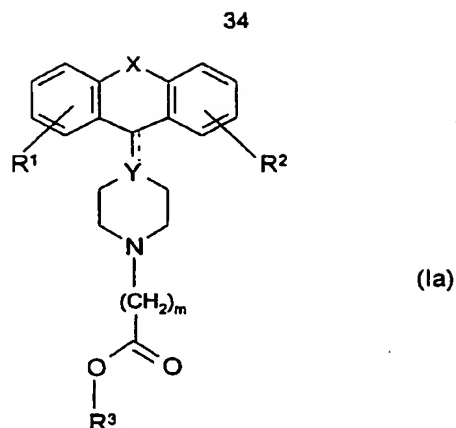
Y is C or N;

- 15 --- is optionally a single bond or a double bond, and --- is a single bond when Y is N;
m is 1, 2, 3, 4, 5 or 6; and
Z is $-\text{COOR}^3$ or



- 20 wherein R^3 is H or C_{1-6} -alkyl; or
a pharmaceutically acceptable salt thereof.

2. A compound of formula Ia

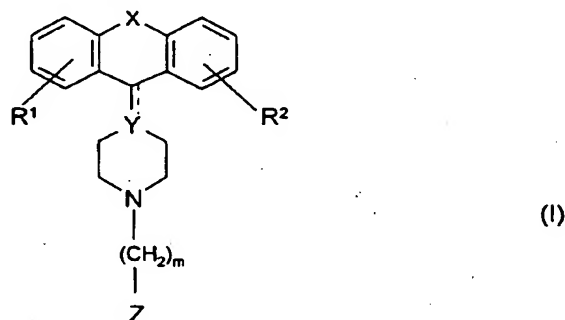


wherein R^1 and R^2 independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy;

- 5 X is ortho-phenylene, -O-, -S-, $-C(R^6R^7)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10})CH_2-$, $-CH_2CH(R^{10})-$, $-(C=O)-$, $-N(R^9)-$ or $-(S=O)-$ wherein R^6 , R^7 , R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl; and wherein R^{10} is C_{1-6} -alkyl or phenyl;
- 10 Y is C or N;
 ____ is optionally a single bond or a double bond, and ____ is a single bond when Y is N;
 m is 1, 2, 3, 4, 5 or 6; and
 R^3 is H or C_{1-6} -alkyl; or
 a pharmaceutically acceptable salt thereof.

15

3. A compound of formula I



wherein R¹ and R² independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy;

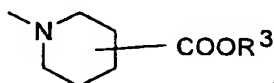
X is ortho-phenylene, -O-, -S-, -C(R⁶R⁷)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R¹⁰)CH₂-, -CH₂CH(R¹⁰)-, -(C=O)-, -N(R⁹)- or -(S=O)- wherein R⁶, R⁷, R⁸ and R⁹ independently are hydrogen or C₁₋₆-alkyl, and wherein R¹⁰ is C₁₋₆-alkyl or phenyl;

Y is C or N;

_____ is optionally a single bond or a double bond, and _____ is a single bond when Y is N;

10 m is 1, 2, 3, 4, 5 or 6; and

Z is -COOR³ or



wherein R³ is H or C₁₋₆-alkyl, provided that when R¹ and R² are hydrogen; X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-; Y is C and _____ is a double bond; m is 1, 2, 3, 4, 5 or 6, then Z is not -COOR³ wherein R³ is H or C₁₋₆-alkyl; or a pharmaceutically acceptable salt thereof.

4. A compound according to anyone of the preceding claims wherein R¹ and R² are selected from hydrogen, halogen, trifluoromethyl or C₁₋₆-alkyl, preferably hydrogen.

5. A compound according to anyone of the preceding claims wherein m is 1, 2, 3 or 4.

6. A compound according to anyone of the preceding claims wherein X is selected from -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂- or -CH₂-S-.

7. A compound according to anyone of the preceding claims wherein X is -CH₂CH₂-.

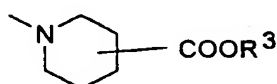
8. A compound according to anyone of the preceding claims wherein Y is N.

9. A compound according to anyone of the preceding claims wherein Z is -COOH.

10. A compound according to anyone of the claims 1 through 6 wherein X is -S-CH₂- or -CH₂-S-.

11. A compound according to anyone of the claims 1 through 6 wherein Y is C and is
5 a double bond.

12. A compound according to anyone of the claims 1 through 6 wherein Z is



10 wherein R³ is H.

13. A compound selected from the following:

15 2-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)acetic acid,

3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)propionic acid,

4-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)butyric acid,

20 5-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl)pentanoic acid,

or a pharmaceutically acceptable salt thereof.

14. A compound selected from the following:

25

1-(3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidinyl)-1-propyl)-3-piperidinecarboxylic acid,

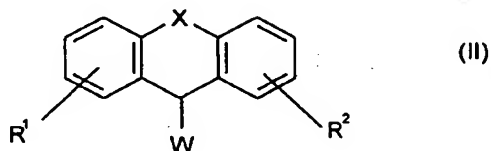
30 (R)-1-(2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)piperidin-1-yl)ethyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

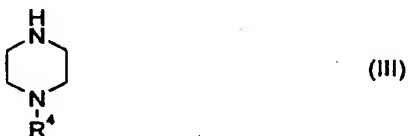
37

15. A method of preparing a compound of formula I, characterized in

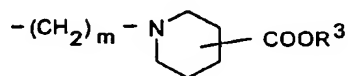
a) reacting a compound of formula II



wherein R^1 , R^2 and X are as defined above and W is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate, with a compound of formula III

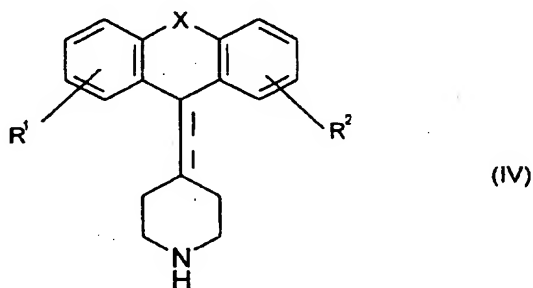


wherein R^4 is hydrogen, a suitable N-protecting group, $-(CH_2)_m-CO_2R^3$ or

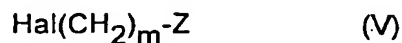


and m and R^3 are as defined above, to form a compound of formula I, or

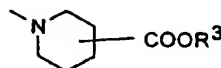
b) reacting a compound of formula IV



wherein R^1 , R^2 and X are as defined above, with a compound of formula V



- 5 wherein Hal is a halogen, Z is $-\text{COOR}^3$ or

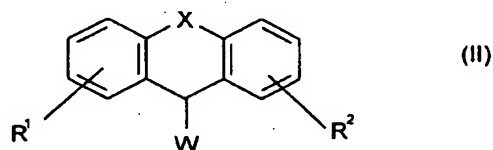


and R^3 and m are as defined above, to form a compound of formula I.

16. A method of preparing a compound of formula Ia, characterized in

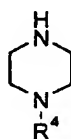
10

a) reacting a compound of formula II



wherein R^1 , R^2 and X are as defined above and W is a suitable leaving group such as

- 15 halogen, p-toluene sulphonate or mesylate, with a compound of formula III

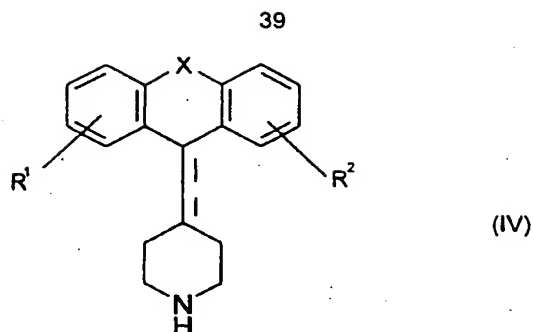


(III)

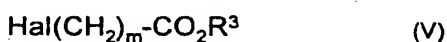
wherein R^4 is hydrogen, a suitable N-protecting group or $-(\text{CH}_2)_m\text{-COOR}^3$ and m and R^3 are

- 20 as defined above, to form a compound of formula Ia, or

b) reacting a compound of formula IV



wherein R¹, R² and X are as defined above, with a compound of formula V



5

wherein Hal means a halogen and R³ and m are as defined above, to form a compound of formula Ia.

17. A pharmaceutical composition comprising as active component a compound
10 according to any of the claims 1 through 14 together with a pharmaceutically carrier or diluent.

18. A pharmaceutical composition suitable for treating neurogenic inflammation
comprising an effective amount of a compound according to any of the claims 1 through 14
15 together with a pharmaceutically acceptable carrier or diluent.

19. A pharmaceutical composition suitable for treating neuropathy comprising an
effective amount of a compound according to any of the claims 1 through 14 together with a
pharmaceutically acceptable carrier or diluent.

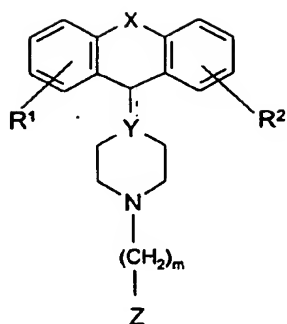
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20. A pharmaceutical composition suitable for treating rheumatoid arthritis comprising an
effective amount of a compound according to any of the claims 1 through 14 together with a
pharmaceutically acceptable carrier or diluent.

21. A pharmaceutical composition suitable for treating insulin resistance comprising an
effective amount of a compound according to any of the claims 1 through 14 together with a
pharmaceutically acceptable carrier or diluent.

22. A pharmaceutical composition suitable for treating non-insulin-dependent diabetes mellitus comprising an effective amount of a compound according to any of the claims 1 through 14 together with a pharmaceutically acceptable carrier or diluent.
- 5 23. The pharmaceutical composition according to claims 17, 18, 19, 20, 21 and 22 comprising between 0.5 mg and 1000 mg of the compound according to any of the claims 1 through 14 per unit dose.
- 10 24. A method of treating insulin resistance in a subject in need of such treatment comprising administering to said subject an effective amount of a compound according to any of the claims 1 through 14.
- 15 25. A method of treating insulin resistance in a subject in need of such treatment comprising administering to said subject a pharmaceutical composition according to claim 24.
26. The use of a compound according to any of the claims 1 through 14 for preparing a pharmaceutical composition for the treatment of neurogenic inflammation.
- 20 27. The use of a compound according to any of the claims 1 through 14 for preparing a pharmaceutical composition for the treatment of neuropathy.
- 25 28. The use of a compound according to any of the claims 1 through 14 for preparing a pharmaceutical composition for treatment of rheumatoid arthritis.
29. The use of a compound according to any of the claims 1 through 14 for preparing a pharmaceutical composition for the treatment of insulin resistance.
- 30 30. The use of a compound according to any of the claims 1 through 14 for preparing a pharmaceutical composition for the treatment of non-insulin-dependent diabetes mellitus.
31. The use of a compound of formula I

41



(I)

wherein R^1 and R^2 are hydrogen;

X is $-O-$, $-S-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-\text{CH}_2-$ or $-\text{CH}_2-\text{S}-$;

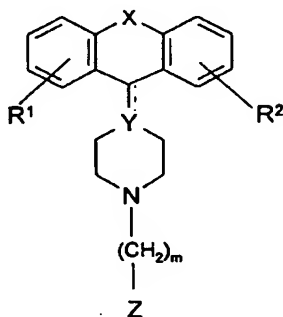
Y is C and --- is a double bond;

5 m is 1, 2, 3, 4, 5 or 6;

Z is $-\text{COOR}^3$ and R^3 is H or C_{1-6} -alkyl, or

a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for treating neurogenic inflammation.

10 32. The use of a compound of formula I



(I)

wherein R^1 and R^2 are hydrogen;

X is $-O-$, $-S-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-\text{CH}_2-$ or $-\text{CH}_2-\text{S}-$;

15 Y is C and --- is a double bond;

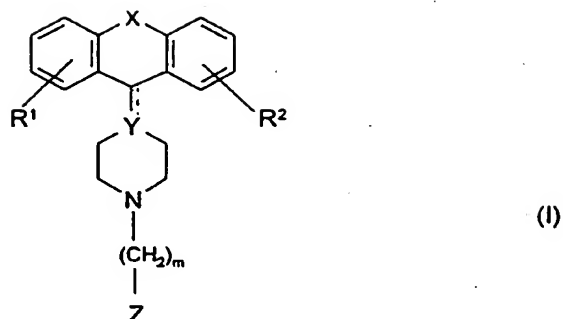
m is 1, 2, 3, 4, 5 or 6;

Z is $-\text{COOR}^3$ and R^3 is H or C_{1-6} -alkyl, or

a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for treating neuropathy.

20

33. The use of a compound of formula I



wherein R^1 and R^2 are hydrogen;

X is $-O-$, $-S-$, $-CH_2CH_2-$, $-CH=CH-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$;

5 Y is C and --- is a double bond;

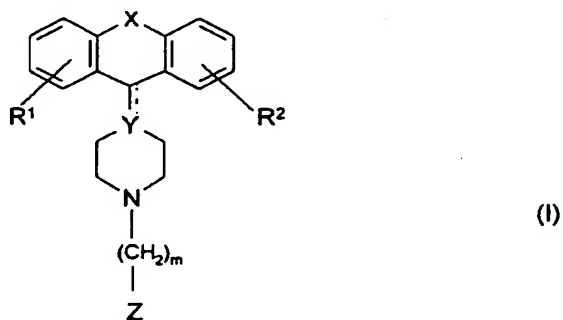
m is 1, 2, 3, 4, 5 or 6;

Z is $-COOR^3$ and R^3 is H or C_{1-6} -alkyl, or

a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for treating rheumatoid arthritis.

10

34. The use of a compound of formula I



wherein R^1 and R^2 are hydrogen;

15 X is $-O-$, $-S-$, $-CH_2CH_2-$, $-CH=CH-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$;

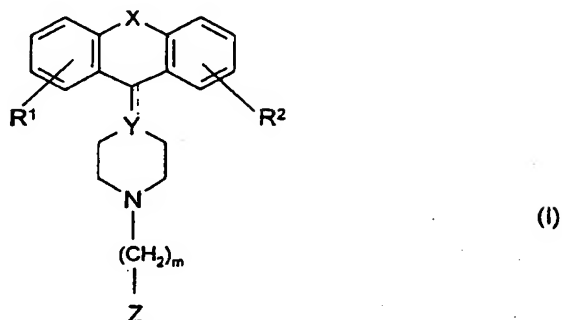
Y is C and --- is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is $-COOR^3$ and R^3 is H or C_{1-6} -alkyl, or

a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for
20 reducing blood glucose.

35. The use of a compound of formula I



wherein R^1 and R^2 are hydrogen;

5 X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

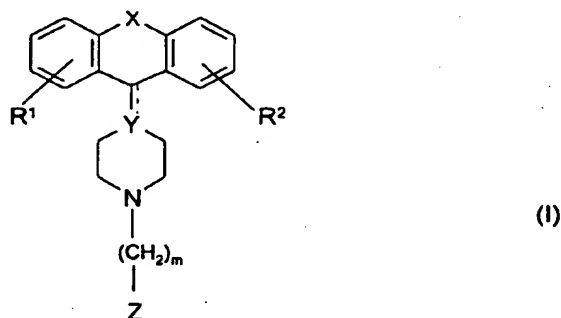
Y is C and is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or

10 a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for treating insulin resistance.

36. The use of a compound of formula I



15 wherein R^1 and R^2 are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

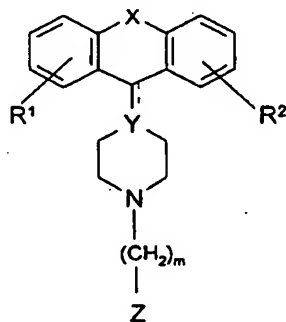
Y is C and is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or

20 a pharmaceutically acceptable salt thereof, for preparing a pharmaceutical composition for treating non-insulin-dependent diabetes mellitus (NIDDM).

37. The use according to any of the claims 31 through 36 wherein X is $-\text{CH}_2\text{CH}_2-$, $-\text{S}-\text{CH}_2-$ or $-\text{CH}_2-\text{S}-$.
- 5 38. The use according to any of the claims 31 through 37 wherein m is 1, 2 or 3.
39. The use according to any of the claims 31 through 38 wherein R^3 is H.
40. The use according to any of the claims 31 through 39 wherein the compound is
10 selected from
- 3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidine)propionic acid,
- 2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidiny)acetic acid,
15 4-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidiny)butyric acid,
- 3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine)propionic acid,
- 20 or a pharmaceutically acceptable salt thereof.
41. The use according to any of the claims 31 through 40 wherein said compound is administered in a range between 0.5 and 1000 mg of the compound per unit dose.
- 25 42. A method for treating neurogenic inflammation in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of formula I



wherein R^1 and R^2 are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

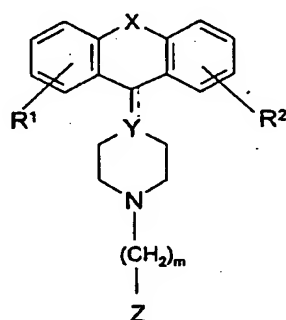
Y is C and ____ is a double bond;

m is 1, 2, 3, 4, 5 or 6;

- 5 Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or
a pharmaceutically acceptable salt thereof.

43. A method for treating neuropathy in a subject in need of such treatment comprising
administering to said subject an effective amount of a compound of formula I

10



wherein R^1 and R^2 are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

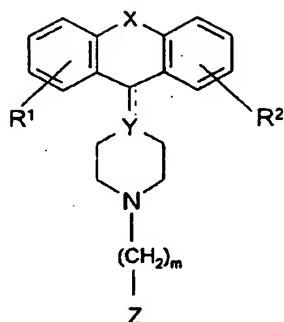
Y is C and ____ is a double bond;

- 15 m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or
a pharmaceutically acceptable salt thereof.

44. A method for treating rheumatoid arthritis in a subject in need of such treatment
20 comprising administering to said subject an effective amount of a compound of formula I

46



(I)

wherein R^1 and R^2 are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

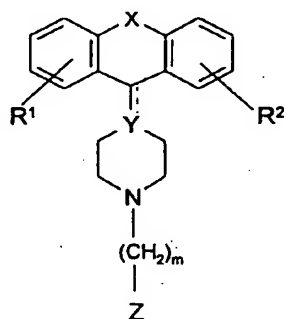
Y is C and ____ is a double bond;

5 m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or

a pharmaceutically acceptable salt thereof.

45. A method for reducing blood glucose in a subject in need of such treatment
 10 comprising administering to said subject an effective amount of a compound of formula I



(I)

wherein R^1 and R^2 are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

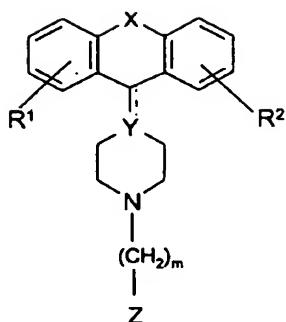
15 Y is C and ____ is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or

a pharmaceutically acceptable salt thereof.

- 20 46. A method for treating insulin resistance in a subject in need of such treatment
 comprising administering to said subject an effective amount of a compound of formula I



(I)

wherein R¹ and R² are hydrogen;

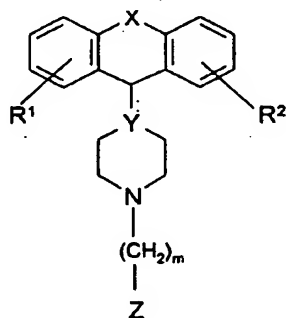
X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

5 Y is C and is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or
a pharmaceutically acceptable salt thereof.

- 10 47. A method for treating non-insulin-dependent diabetes mellitus (NIDDM) in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of formula I



(I)

15 wherein R¹ and R² are hydrogen;

X is -O-, -S-, -CH₂CH₂-, -CH=CH-, -O-CH₂-, -CH₂-O-, -S-CH₂- or -CH₂-S-;

Y is C and is a double bond;

m is 1, 2, 3, 4, 5 or 6;

Z is -COOR³ and R³ is H or C₁₋₆-alkyl, or

20 a pharmaceutically acceptable salt thereof.

48

48. A method according to any of the claims 42 through 47 wherein X is -CH₂CH₂-, -S-CH₂- or -CH₂-S-.

49. A method according to any of the claims 42 through 48 wherein m is 1, 2 or 3.

5

50. A method according to any of the claims 42 through 49 wherein R³ is H.

51. A method according to any of the claims 42 through 50 wherein the compound is selected from

10

3-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidine)propionic acid,

2-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidiny)acetic acid,

15 4-(4-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-piperidiny)butyric acid,

3-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine)propionic acid,

or a pharmaceutically acceptable salt thereof.

20

52. A method according to any of the claims 42 through 51 wherein said compound is administered in a range between 0.5 and 1000 mg of the compound per unit dose.

53. Any novel feature or combination of features as described herein.

25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00271

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 295/108, C07D 211/70, C07D 409/04, C07D 409/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. Pharm. Bull., Volume 42, No 11, November 1994, Nobuhiko Iwasaki et al, "Amphoteric Drugs. II. Synthesis and Antiallergic Activity of (4-(5H-Dibenzo(a, d)cyclohepten-5-ylidene)piperidino)alkanoic Acid Derivatives and Related Compounds" page 2285 - page 2290 --	1-2,4-7, 9-11,15-23, 53
X	EP 0406739 A2 (HOKURIKU PHARMACEUTICAL CO., LTD.), 9 January 1991 (09.01.91) --	1-2,4-7, 9-11,15-23, 53
X	DE 2256392 A (SANDOZ AG), 30 May 1973 (30.05.73) --	1-2,4-6,11, 15-23,53

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 Sept 1998

Date of mailing of the international search report

08-10-1998

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00271

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0451772 A1 (HOKURIKU PHARMACEUTICAL CO., LTD.), 16 October 1991 (16.10.91) --	1-2,4-6, 9-11,15-23, 53
A	EP 0682015 A1 (AJINOMOTO CO., INC.), 15 November 1995 (15.11.95) --	1-23,26-41, 53
A	WO 9220658 A1 (NOVO NORDISK A/S), 26 November 1992 (26.11.92) -- -----	1-23,26-41, 53

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00271

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24-25, 42-52
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

27/07/98

International application No.

PCT/DK 98/00271

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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